IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES
(Attorney Docket No. ACY33464 D1)

In re Application of:	)	Appln. No.: 10/055,502
	)	Confirmation No.: 8971
JEREMY I. LEVIN *et al.*	)	Customer No.: 25291
	)	Group Art Unit: 1625
Filed: 11/13/2001	)	Examiner: D. Margaret Seaman
	)	
For: ALKYNYL CONTAINING HYDROXAMIC ACID COMPOUNDS AS MATRIX METALLO-PROTEINASE AND TACE INHIBITORS	)	Paper No.: 15

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

05/06/2004 SSESHE1 00000093 011300 10055502
01 FC:1402 330.00 DA

APPELLANTS' BRIEF UNDER 37 C.F.R. § 1.192(a)

Dear Sir:

This is an appeal in the above-referenced patent application from the decision of the Primary Examiner mailed September 4, 2003 making a final rejection of Claims 1, 2 and 5-7. Appellants' brief in support of the appeal is being submitted in triplicate. Payment of the statutory fee for filing this brief is arranged in the Transmittal Letter. No oral hearing is requested.

(1) *Real Party in Interest*

The real party in interest is the assignee of record. Wyeth Holdings Corporation (formerly American Cyanamid Company), having an office at Five Giralda Farms, Madison, New Jersey 07940, is the assignee of any patent issuing from the application.

(2) *Related Appeals and Interferences*

There are no other appeals or interferences known to Appellants, Appellants' legal representative or assignee that will directly affect, be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) *Status of Claims*

Claims 1, 2 and 5-7 are pending in the subject application, stand rejected by the Examiner and are the subject of this appeal. Claims 3 and 4 have been canceled by amendment.

ANNE M. ROSENBLUM ATTORNEY AT LAW
163 DELAWARE AVENUE - SUITE 212 • DELMAR, NEW YORK 12054 • TELEPHONE: (518) 475-0611

(4) *Status of Amendments*

An amendment dated December 4, 2003 was filed subsequent to the final rejection and has been entered in the record. The amendment removed nonelected subject matter from the pending claims in compliance with the Examiner's requirement in the final rejection to do so.

(5) *Summary of Invention*

Appellants' invention defined in the claims, which are involved in the appeal, is drawn to novel non-peptide inhibitors of the matrix metalloproteinase ("MMP") enzymes and the TNF-α converting enzyme ("TACE"), methods of inhibiting pathological changes mediated by TACE by the administration of the inhibitors and pharmaceutical compositions comprising the inhibitors, in which the inhibitors have a general formula I wherein Y is heteroaryl. Reference to the present invention may be found in the specification from page 7, line 9, to page 8, line 15. Some preferred heteroaryl embodiments of Y in the present invention are identified as pyridyl, thienyl, furanyl, imidazolyl, triazolyl and thiadiazolyl on page 8, lines 18 and 19. The heteroaryl substituent is more precisely defined and many specific heteroaryl rings of the invention are described from page 16, line 15, to page 17, line 8. A description of how to make representative compounds of formula I (wherein Y is phenyl) is found in Examples 1-125 on pages 36-104 plus 12 general schemes on pages 21-35 of the specification. Discussion on how to use the compounds of the invention as inhibitors of MMP-1, MMP-9, MMP-13 and TACE, the *in vitro* data from tests involving representative phenyl compounds and a variety of pharmaceutical compositions for administration in mammals is found in the application on pages 104-117.

The claims drawn to the analogous phenyl compounds of formula I was granted U.S. Patent No. 6,340,691 B1. The claims of this divisional application involved in the appeal are directed to the heteroaryl derivatives due to a restriction requirement in the parent application.

A copy of the claims on appeal is appended to this Brief.

(6) *Issues*

(A) <u>The Final Rejection</u>

The two issues presented for appeal are whether Claims 1, 2 and 5-7 are unpatentable under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement; and/or whether Claims 1, 2 and 5-7 are unpatentable under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

ANNE M. ROSENBLUM ATTORNEY AT LAW
163 DELAWARE AVENUE - SUITE 212 • DELMAR, NEW YORK 12054 • TELEPHONE: (518) 475-0611

(B) The References Made of Record

The Examiner did not cite or apply any references in support of the final rejection.

(7) *Grouping of Claims*

Appellants consider that Claims 1, 2 and 5-7 are not separately patentable under the issues at hand and state that the claims stand or fall together on the present record.

(8) *Argument*

(A) The Specification Satisfies the Written Description Requirement

Appellants' heteroaryl derivatives of formula I had been a part of the original set of claims as filed and had been artificially restricted out of the prior application to accommodate administrative convenience for examination purposes. Appellants assert that the specification provides an adequate written description of formula I from page 7, line 9, to page 8, line 15 and sufficiently exemplifies a large number of heteroaryl rings from page 16, line 15, to page 17, line 8 in support of the claimed invention.

Compliance with the statutory requirements of the first paragraph of 35 U.S.C. § 112 is a question of law. With respect to the written description requirement, the Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize a description of the invention defined by the claims in Appellants' disclosure (*In re Wertheim*, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *Ex parte Sorenson*, 3 USPQ2d 1462, 1463 (Bd. Pat. App. & Inter. 1987)). Otherwise, there is a strong presumption in favor of Appellants' position that the specification as filed contains an adequate written description of the claimed invention (*In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976)).

It is submitted that the Examiner, with all due respect, failed to meet the initial burden of proof by not providing any evidence to justify the Office position. The Examiner rejected the claims under 35 U.S.C. § 112, first paragraph, because she found no working examples of a compound wherein Y is a heteroaryl. The Examiner erred by relying solely on this finding without showing proof that the absence of the examples would make a significant difference to an ordinary chemist. The bare conclusion that there is no description of the heteroaryl moiety (Y) that would allow the artisan to recognize that a candidate compound would potentially inhibit the pathological changes mediated by TNF-α converting enzyme ("TACE") lacked substantiating evidence. By failing to state adequate support for the rejection, the Examiner did not satisfy the

ANNE M. ROSENBLUM ATTORNEY AT LAW
163 DELAWARE AVENUE - SUITE 212 • DELMAR, NEW YORK 12054 • TELEPHONE: (518) 475-0611

Office's burden of proof.

Contrary to the Examiner's opinion, Appellants believe that the heteroaryl moiety is adequately disclosed in the written description of the invention. There is ample evidence to establish that Appellants had possession of the heteroaryl compounds that inhibit TACE on the date that the application was originally filed in the U.S. Patent and Trademark Office. The pending claims are drawn to a genus of heteroaryl derivatives possessing activity as inhibitors of the MMP enzymes and TACE. The application contains a precise definition of the heteroaryl substituent (pages 16 and 17), a sizeable number of exemplified heteroaryl rings such as pyrrole, furan, thiophene, pyridine, pyrimidine and the like (at the top of page 17), one hundred and twenty-five specific examples of how to prepare a variety of analogous phenyl compounds (pages 36-104) and a detailed explanation of how to use representative compounds of the invention as inhibitors of MMP-1, MMP-9, MMP-13 and TACE (pages 104-117). Indeed, a large group of functionally equivalent species selected from the original genus have actually been prepared and tested.

In addition, the application contains twelve general synthesis schemes on pages 21-35 showing how to attach X as O, S or NHR_7, and A as S, SO or SO_2 on the representative aryl compounds that could readily be applied to heteroaryl in place of the aryl moiety. Scheme 12 illustrates any Y substituent selected from either aryl or heteroaryl (see page 35). Considering the general formula I teaches the functional equivalency of aryl and heteroaryl in the Y position, one of ordinary skill in the art would appreciate that the general teachings in the schemes and working examples apply to the analogous hydroxamic acid derivatives containing heteroaryl as Y.

The Examiner has not given any contrary evidence in the record that would show that the heteroaryl group would be problematic, for example, being unstable or highly reactive, such that replacement of the aryl by heteroaryl would be unpredictable and, therefore, not believable on its face. In fact, the ordinary chemist would consider that the aryl and the heteroaryl are interchangeable in the Y position of the present core structure for many reasons. Looking at the original formula of the present invention as filed, the positions of R_1, R_5, R_8, R_9, R_{10}, R_{11} and R_{12} include both aryl and heteroaryl among the members of each group. Many of the disclosed heteroaryls, such as benzothiophene, pyrrole, isoquinoline, quinoline, isoindol and the like, have been exemplified and shown to possess TACE inhibiting activity in a variety of positions on the molecule. Based on the interchangeability of aryls and heteroaryls in the representative phenyl

ANNE M. ROSENBLUM ATTORNEY AT LAW
163 DELAWARE AVENUE - SUITE 212 • DELMAR, NEW YORK 12054 • TELEPHONE: (518) 475-0611

compounds, it is reasonable to conclude that Y can also be heteroaryl, as disclosed in the written description, without adversely affecting the integrity and activity of the compounds of the invention.

Moreover, the present compounds are part of a series of novel acetylenic sulfonamide hydroxamic acid and thiol compounds that possess TACE inhibiting activity. Many of these TACE inhibiting compounds are patented in U.S. Patent Nos. 6,326,516 B1 ("Exhibit A"); 6,313,123 B1 ("Exhibit B"); 6,225,311 B1 ("Exhibit C"); and 6,200,996 B1 ("Exhibit D"). Aryl (as aryl, phenyl or naphthyl) and heteroaryl in similar Y positions are claimed in several hydroxamic acid structures exhibiting TACE inhibiting activity. Most importantly, in many applications comprising this series of patented compounds, the Office did not restrict the aryl and heteroaryl derivatives as separate inventions giving credence to the functional equivalency of these two substituents in the present genus. The patent claims demonstrate that it is conceivable on the filing date of the present application that aryl and heteroaryl are interchangeable without adversely affecting the integrity of the structure or the TACE inhibiting properties of the compound. Since the claimed genus is described in the subject application as originally filed, one of ordinary skill in the art would have no reason not to believe Appellants' assertion that aryl and heteroaryl are comparable moieties at the Y position. The interchangeability of aryl and heteroaryl would be believable on its face.

In conclusion, the Examiner erred by relying totally on the absence of working examples and by ignoring the positive teachings in the application, taken as a whole. The written description exemplifies heteroaryl as Y in formula I on page 7, line 13 and the description teaches what to select as the heteroaryl ring from page 16, line 15, to page 17, line 8. Taking the extensive definitions into consideration, it is clear that the chemist would recognize that the Appellants were in possession of the necessary common attributes exhibited by the entire genus on the filing date of the present application. Without any doubt, persons having ordinary skill in the art would recognize a description of the invention defined by the claims in Appellants' disclosure. Hence, the Examiner failed to meet the Office's burden of proof and was not justified in sustaining the rejection based on lack of written description.

(B) The Specification Satisfies the Enablement Requirement

The legal question of enablement involves an assessment of whether a patent disclosure would have enabled one of ordinary skill in the art at the time the application was filed to make and use the claimed invention without undue experimentation (*Hybritech Inc. v. Monoclonal*

ANNE M. ROSENBLUM ATTORNEY AT LAW
163 DELAWARE AVENUE - SUITE 212 • DELMAR, NEW YORK 12054 • TELEPHONE: (518) 475-0611

Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986); *In re Wands*, 858 F.3d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

To resolve the pivotal question of whether the practice of the claimed invention would involve undue experimentation, many of the usual factors appeared to be considered at first glance of the Examiner's factual determination in the record. It is believed, however, that the Examiner, with all due respect, actually based the rejection on a single fact and sole reason that there are no specific examples of any compound in the specification wherein Y is a heteroaryl. Other essential factors were stated but glossed over in the final analysis. The Examiner failed to cite any source in support of the Office position that would lead one to conclude that the ordinary chemist would not be able to substitute the heteroaryl substituent for an aryl and reasonably expect the claimed genus to exhibit TACE inhibiting properties. Consequently, it is submitted that the Examiner's interpretation of the proffered data and the conclusion based on the facts were clearly erroneous. Appellants provided evidence to show that it was reasonable to assume that one could extrapolate the data of the numerous examples of aryl compounds to include the heteroaryl compounds of the claimed invention. The Examiner erred by not giving adequate weight to Appellants' evidence.

The standard factors of enablement as applied to the case at hand are as follows:

1) The breadth of the claims:

Contrary to the Examiner's belief, the genus claim cannot be considered broad. The same formula having C(O)N(OH) or C≡C as the common core has been allowed under U.S. Patent No. 6,340,691 B1, thereby refuting any contention that the claims are extremely broad. The only difference between the patented formula and the present genus lies in the single replacement of heteroaryl for aryl at one position Y on the structure. This single modification does not make the claims overly broad.

2) The nature of the invention:

The Examiner correctly asserts that the invention is drawn to compounds and methods of inhibiting pathological changes mediated by TACE. However, under the nature of the invention, it should also be pointed out that the patented compounds and the genus of this divisional application, together as originally filed, contain a wide variety of heteroaryl rings at different positions that do not alter the TACE inhibiting properties of the compounds.

ANNE M. ROSENBLUM ATTORNEY AT LAW
163 DELAWARE AVENUE - SUITE 212 • DELMAR, NEW YORK 12054 • TELEPHONE: (518) 475-0611

3) The state of the prior art:

Appellants agree with the Examiner's finding that the prior art knows of compounds that inhibit TACE but none with the same core as is instantly claimed. As a consequence, there is no art that precludes patenting the claimed genus.

4) The level of one of ordinary skill:

The Examiner omitted the level of one of ordinary skill from the analysis in the record when this factor should be taken into consideration in support of Appellants' position on patentability. As the Examiner has admitted elsewhere, there are compounds known in the art that inhibit TACE as well as the MMP enzymes. This is not a totally new area of chemistry. See, for example, the research highlighted in the background of the invention on pages 2-6 of the specification and in particular, the disclosure on pages 3-6 of inhibitors of MMP as sulfone hydroxamic acids, sulfonyl acetohydroxamic acids, piperidine sulfone hydroxamic acids and the like.

5) The level of predictability in the art:

The Examiner asserts that the predictability in the art is unknown due to the lack of art that has similar compounds that work. It is believed that the Examiner erred by misinterpreting the extensive data within Appellants' disclosure and making a wrong conclusion based on a blanket presumption of unknown predictability in the chemical arts. This predictability factor refers to the ability of the ordinary chemist to extrapolate the disclosed results to the claimed invention. It does not require a disclosure of every operable species or exemplification of each and every embodiment. The predictability factor only determines if the ordinary chemist would have reasonable doubt as to the accuracy of aryl and heteroaryl being comparable within the context of this invention. The Examiner has not given any scientific principle or literature reference to validate any reasonable doubt or refute the Appellants' position that the aryl and heteroaryl are interchangeable. Furthermore, the Examiner ignored the evidence presented by the Appellants that the aryl and heteroaryl substituents are shown to be equivalent for purposes of this invention by virtue of several positions (R_1, R_5, R_8, R_9, R_{10}, R_{11} and R_{12}) encompassing both aryl and heteroaryl among the members of each group. Many of the disclosed heteroaryls, such as benzothiophene, pyrrole, isoquinoline, quinoline, isoindol and the like, were exemplified and shown to possess TACE inhibiting activity in a variety of positions on the molecule. Based on the interchangeability of aryls and heteroaryls in the representative phenyl compounds of the working

ANNE M. ROSENBLUM ATTORNEY AT LAW
163 DELAWARE AVENUE - SUITE 212 • DELMAR, NEW YORK 12054 • TELEPHONE: (518) 475-0611

examples, the ordinary chemist would not doubt that the Y group could also be heteroaryl as taught in the application. The chemist would not expect that the heteroaryl in the Y position would adversely affect the integrity and activity of the compounds of the invention.

6) The amount of direction provided by the inventor:

The Examiner asserts that the inventor provides no direction for the ordinary artisan to take other than Y needs to be phenyl. This is not true. The description of the claimed genus on page 8, line 13, of the application recites Y as aryl or heteroaryl. The application further discloses on page 8, lines 18 and 19, that Y is phenyl, pyridyl, thienyl, furanyl, imidazolyl, triazolyl and thiadiazolyl in some preferred embodiments of the invention and, on pages 16 and 17, the application exemplifies a large number of heteroaryl rings. In sum, the disclosure supplies an adequate definition of the term "heteroaryl" to apprise the ordinary chemist of what to select in place of phenyl at the Y position. Moreover, the application contains one hundred and twenty-five specific examples of how to prepare a variety of functionally equivalent phenyl compounds (pages 36-104) and how to use the representative compounds of the invention as inhibitors of MMP-1, MMP-9, MMP-13 and TACE (pages 104-117) including standard pharmacological test procedures. There are twelve general schemes (pages 21-35) illustrating how to make the attachment of X as O, S or NHR_7, and A as S, SO or SO_2 in which the heteroaryl may substitute for the representative aryl compound. Scheme 12 illustrates any Y substituent selected from aryl or heteroaryl (see page 35). Appellants have provided sufficient guidance to the public to enable one to practice and use the claimed invention without undue effort.

7) The existence of working examples:

The Examiner maintains that there are no examples, either working or not working, in the specification wherein Y is heteroaryl. This is not true. The selection of the heteroaryl moiety is fully exemplified in great detail on pages 16 and 17 of the application and a large group of functionally equivalent species selected from the original genus have actually been prepared and tested. Consequently, it is believed that the Examiner has not analyzed what the application, taken as a whole, actually teaches one of ordinary skill in the art. The Examiner is ignoring the fact that the application shows how to make and use several different, functionally equivalent phenyl compounds. The ordinary chemist would know exactly what steps to take to substitute a heteroaryl for the illustrated phenyl and successfully make the claimed compounds without

ANNE M. ROSENBLUM ATTORNEY AT LAW
163 DELAWARE AVENUE - SUITE 212 • DELMAR, NEW YORK 12054 • TELEPHONE: (518) 475-0611

undue experimentation. Based on the disclosure of the TACE inhibiting properties of nearly one hundred and twenty-five phenyl compounds, the chemist would expect the analogous heteroaryl derivatives to possess TACE inhibiting activity. There is nothing in the record to suggest otherwise.

8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure:

The Examiner thinks that the quantity of experimentation needed to make and use the instant invention is unexpected but has not given any evidence to sustain the Office position. It cannot be ignored that the heteroaryl group had been artificially restricted out of the parent application for administrative convenience in searching and examining the aryl derivatives. However, on the date of filing the original application intact, the content of the disclosure provided a sufficient number of species to support the entire genus including the present genus drawn to the analogous heteroaryl substituents. Appellants believe that the application provides sufficient guidance through the general schemes and the numerous examples to enable one of ordinary skill in the art to practice the claimed invention without an unexpected quantity of experimentation.

In sum, the chemist will comprehend without any doubt that the heteroaryl can substitute for phenyl and will reasonably expect to find the TACE inhibiting activity from the heteroaryl derivatives. The amount of experimentation that it would take to replace the illustrated phenyl substituent with one of the heteroaryl groups, which are described fully on pages 16 and 17, would merely be routine. It is well within the ordinary skill of the chemical and pharmaceutical arts to be able to handle this level and type of chemistry. The specification clearly enables the ordinary artisan to be able to practice the claimed invention. As a consequence, the Examiner failed to meet the Office's burden of proof and had no reasonable basis to sustain the rejection based on lack of enablement.

(C) Aryl and Heteroaryl Are Functionally Equivalent Substituents

It is submitted that aryl and heteroaryl are functionally equivalent substituents that can readily substitute for each other on the Y position of the claimed genus. There is a strong correlation between structure and function in the specification that would yield the desired biological properties. During prosecution, Appellants proffered evidence in good faith that on the filing date of the application, the chemist would be able to predict the TACE inhibiting activity and

ANNE M. ROSENBLUM ATTORNEY AT LAW
163 DELAWARE AVENUE - SUITE 212 • DELMAR, NEW YORK 12054 • TELEPHONE: (518) 475-0611

appreciate how to use the claimed compounds without undue experimentation based on the disclosure of the TACE inhibiting properties of almost one hundred and twenty-five phenyl compounds, their own published work of similar phenyl and pyridyl compounds in U.S. Patent No. 6,225,311 B1 ("Exhibit C"), and the further structure-activity relationship shown by similar compounds in Exhibits A-D. It is now appreciated that all four patents have the same effective filing date as the present application (January 27, 1999) and cannot be used to show a prior, known structure-activity relationship.

Appellants therefore submit supplemental evidence of the functional equivalency of aryl and heteroaryl moieties in prior U.S. patents having filing dates before January 27, 1999. There are many patents that prove a prior, known structure-activity relationship in MMP and TACE inhibiting compounds. Notably, key positions on the patented structures are drawn to both aryl and heteroaryl substituents. Attention is respectfully drawn to the claims of U.S. Patent Nos. 5,929,097; 5,962,481; 5,977,408; 6,162,814; 6,162,821; 6,197,791; 6,331,563; 6,441,023; and 6,462,073, to name only a few. As an example of this series, a true copy of the claims of U.S. Patent No. 5,929,097 is attached herewith ("Exhibit E").

Nevertheless, the four related U.S. patents of Exhibits A-D can establish that, as of the filing date of the present application, a skilled artisan like the inventors would consider that aryl and heteroaryl are interchangeable in TACE inhibiting compounds without anticipating any detrimental effect. Taken in view of the patented aryl compounds in the issued parent U.S. Patent No. 6,340,691 B1, the series of MMP and TACE inhibiting compounds also show that it is reasonable to conclude that the experimentation to make and use the claimed genus of the analogous heteroaryl derivatives on the effective filing date of the application would be routine. All of the noted patents show that one of ordinary skill in the art has reason to trust that Appellants' assertions on the date of filing the subject application are true and no reason to doubt the truth that Y can be either aryl or heteroaryl.

Although the Examiner kindly reviewed Appellants' demonstration of the TACE inhibiting activity of two patented compounds from Exhibit C, the Examiner then erred by misinterpreting the data and not giving adequate weight to Appellants' evidence. It is submitted that the Examiner did not find the evidence persuasive because she drew the wrong conclusion from the showing. She had observed that the pyridine compound was more than four times the activity of phenyl and then held

ANNE M. ROSENBLUM ATTORNEY AT LAW
163 DELAWARE AVENUE - SUITE 212 • DELMAR, NEW YORK 12054 • TELEPHONE: (518) 475-0611

that the activities were very different for small differences between the structures. Contrary to the Examiner's opinion, the proof shows that both patented compounds provide potent TACE inhibiting activity at very low TACE IC_{50} values of 7 nM (phenyl) and 29 nM (pyridyl), with the phenyl compound being slightly more potent. In addition, both patented compounds are utilized in the patented method of inhibiting pathological changes mediated by TACE (U.S. Patent No. 6,225,311 B1, claim 10, col. 207, line 38 to col. 208, line 48).

With all due respect, the Examiner missed the whole point of the proffered data. Appellants wanted to substantiate that aryl (phenyl) and heteroaryl (pyridine) are interchangeable substituents and to prove that the heteroaryl derivative would retain the TACE inhibiting properties of the aryl substituent in related TACE inhibiting compounds. Most importantly for the issues at hand, the data establish that it is reasonable to expect that the TACE inhibiting activity of the phenyl substituent will correlate to useful TACE inhibiting activity of the heteroaryl substituent. The data clearly show that the ordinary chemist can extrapolate biological activity from the results of the aryl compounds and predict similar TACE inhibiting activity of the heteroaryl derivatives. There is no question that aryl and heteroaryl are functionally equivalent for purposes of the claimed invention. Thus, the rejection of the pending claims under 35 U.S.C. § 112, first paragraph, is not justified and should not be sustained.

ANNE M. ROSENBLUM ATTORNEY AT LAW
163 DELAWARE AVENUE - SUITE 212 • DELMAR, NEW YORK 12054 • TELEPHONE: (518) 475-0611

CONCLUSION

For the reasons discussed above and during prosecution, the Examiner's decision rejecting Claims 1, 2 and 5-7 under 35 U.S.C. § 112, first paragraph, should be reversed and the pending claims under appeal should be allowed.

Respectfully submitted,

WYETH HOLDINGS CORPORATION

Date: May 4, 2004

By: Anne M Rosenblum
Anne M. Rosenblum
Attorney for Appellants
Registration No. 30,419

Attorney of Record and Post Office
Address To Which Correspondence
Is To Be Sent:

John W. Hogan, Jr., Esq.
Wyeth
Patent Law Department
Five Giralda Farms
Madison, New Jersey 07940

FILING BY EXPRESS MAIL UNDER 37 C.F.R. § 1.10

This brief on appeal is being deposited in triplicate with the U.S. Postal Service on May 4, 2004 to be delivered by the "Express Mail Post Office to Addressee" service under Mailing Label Number EU730354156US addressed to: MS Appeal Brief - Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

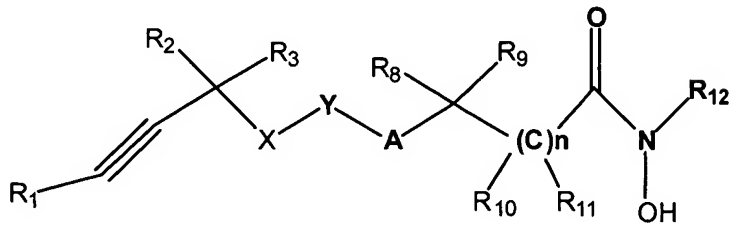
Anne M Rosenblum
Anne M. Rosenblum

ANNE M. ROSENBLUM ATTORNEY AT LAW
163 DELAWARE AVENUE - SUITE 212 • DELMAR, NEW YORK 12054 • TELEPHONE: (518) 475-0611

(9) *APPENDIX*

THE CLAIMS INVOLVED IN THE APPEAL

Claim 1. A compound of formula



wherein:

R_1 is hydrogen, aryl, heteroaryl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or C_5-C8-cycloheteroalkyl having from 1-2 heteroatoms selected from N, NR_7, S and O;

R_2 and R_3 are each independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or –CCH;

R_5 is hydrogen, alkyl of 1-8 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, heteroaryl, or C4-C8-cycloheteralkyl;

R_7 is hydrogen, aryl, aralkyl, alkyl of 1-6 carbon atoms, or cycloalkyl of 3-6 carbon atoms, oxy, C1-C8 alkanoyl, $COOR_5$, COR_5, -SO_2-C1-C8 alkyl, -SO_2-aryl, -SO_2-heteroaryl, -CO-NHR_1;

R_8, R_9, R_{10}, and R_{11} are each, independently, hydrogen, aryl, aralkyl, 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR_7, O and S, heteroaralkyl having from 1-3 heteroatoms selected from N, NR_7, O and S, cycloalkyl of 3-6 carbon atoms, -C_4-C_8-cycloheteroalkyl having from 1-3 heteroatoms selected from N, NR_7, O and S, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms;

R_{12} is hydrogen, aryl or 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR_7, S and O, cycloalkyl of 3-6 carbon atoms, -C_5-C8-cycloheteroalkyl having from 1 to 2 heteroatoms selected from N, NR_7, S and O, or alkyl of 1-6 carbon atoms;

A is O, S, SO, SO_2, NR_7, or CH_2;

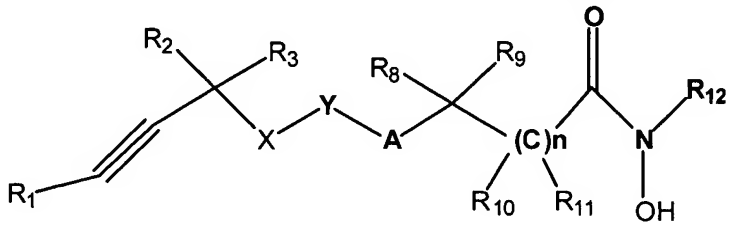
X is O, S, SO, SO_2, NR_7, or CH_2;

Y is heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y; and

n is 0-2; or a pharmaceutically acceptable salt thereof.

Claim 2. A compound according to claim 1 wherein Y is pyridyl, thienyl, furanyl, imidazolyl, triazolyl, or thiadiazolyl.

Claim 5. A method of inhibiting pathological changes mediated by TNF-α converting enzyme (TACE) in a mammal in need thereof which comprises administering to said mammal a therapeutically effective amount of a compound having the formula:



wherein:

R_1 is hydrogen, aryl, heteroaryl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or C5-C8-cycloheteroalkyl having from 1-2 heteroatoms selected from N, NR_7, S and O;

R_2 and R_3 are each independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or –CCH;

R_5 is hydrogen, alkyl of 1-8 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, heteroaryl, or C4-C8-cycloheteralkyl;

R_7 is hydrogen, aryl, aralkyl, alkyl of 1-6 carbon atoms, or cycloalkyl of 3-6 carbon atoms, oxy, C1-C8 alkanoyl, $COOR_5$, COR_5, -SO_2-C1-C8 alkyl, -SO_2-aryl, -SO_2-heteroaryl, -CO-NHR_1;

R_8, R_9, R_{10}, and R_{11} are each, independently, hydrogen, aryl, aralkyl, 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR7, O and S, heteroaralkyl having from 1-3 heteroatoms selected from N, NR_7, O and S, cycloalkyl of 3-6 carbon atoms, -C4-C8-cycloheteroalkyl having from 1-3 heteroatoms selected from N, NR_7, O and S, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms;

R_{12} is hydrogen, aryl or 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR_7, S and O, cycloalkyl of 3-6 carbon atoms, -C5-C8-cycloheteroalkyl having from

1 to 2 heteroatoms selected from N, NR_7, S and O, or alkyl of 1-6 carbon atoms;

A is O, S, SO, SO_2, NR_7, or CH_2;

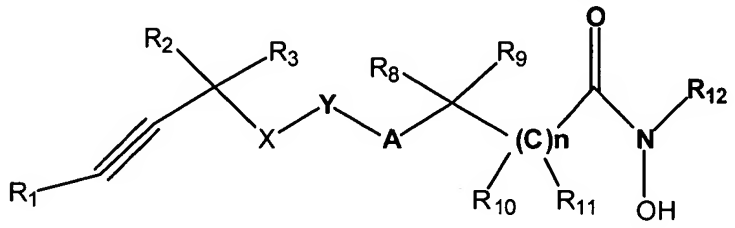
X is O, S, SO, SO_2, NR_7, or CH_2;

Y is heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y; and

n is 0-2; or a pharmaceutically acceptable salt thereof.

Claim 6. The method of Claim 5 wherein the condition treated is rheumatoid arthritis, graft rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease or HIV infection.

Claim 7. A pharmaceutical composition comprising a compound having the formula:



wherein:

R_1 is hydrogen, aryl, heteroaryl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or C_5-C8-cycloheteroalkyl having from 1-2 heteroatoms selected from N, NR_7, S and O;

R_2 and R_3 are each independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or –CCH;

R_5 is hydrogen, alkyl of 1-8 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, heteroaryl, or C4-C8-cycloheteralkyl;

R_7 is hydrogen, aryl, aralkyl, alkyl of 1-6 carbon atoms, or cycloalkyl of 3-6 carbon atoms, oxy, C1-C8 alkanoyl, $COOR_5$, COR_5, -SO_2-C1-C8 alkyl, -SO_2-aryl, -SO_2-heteroaryl, -CO-NHR_1;

R_8, R_9, R_{10}, and R_{11} are each, independently, hydrogen, aryl, aralkyl, 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR7, O and S, heteroaralkyl

having from 1-3 heteroatoms selected from N, NR_7, O and S, cycloalkyl of 3-6 carbon atoms, -C_4-C_8-cycloheteroalkyl having from 1-3 heteroatoms selected from N, NR_7, O and S, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms;

R_{12} is hydrogen, aryl or 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR7, S and O, cycloalkyl of 3-6 carbon atoms, -C_5-C8-cycloheteroalkyl having from 1 to 2 heteroatoms selected from N, NR_7, S and O, or alkyl of 1-6 carbon atoms;

A is O, S, SO, SO_2, NR_7, or CH_2;

X is O, S, SO, SO_2, NR_7, or CH_2;

Y is heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y; and

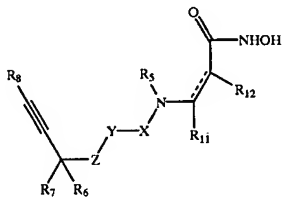
n is 0-2; or a pharmaceutically acceptable salt thereof.

subjectively determined by the attending physician. The variables involved include the severity of the dysfunction, and the size, age, and response pattern of the patient. Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached. Precise dosages for oral, parenteral, nasal, or intrabronchial administration will be determined by the administering physician based on experience with the individual subject treated and standard medical principles.

Preferably the pharmaceutical composition is in unit dosage form, e.g., as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage form can be packaged compositions, for example packed powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

What is claimed:

1. Hydroxamide acids of the formula:



where the C(=O)NHOH moiety and the —NR5- moiety are bonded to adjacent carbons; wherein

X is SO_2 or —P(O)R_{10};

Y is 5–10 membered heteroaryl ring having from 1–3 heteroatoms selected from N, NR9, S and O, phenyl or naphthyl; with the proviso that X and Z may not be bonded to adjacent atoms of Y:

Z is O, NH, CH_2 or S;

R_5 is hydrogen or alkyl of 1–6 carbon atoms;

$R_6$and R_7 are each, independently, hydrogen or methyl;

R_8 is hydrogen, alkyl of 1–6 carbon atoms, alkenyl of 2–6 carbon atoms, alkynyl of 2–6 carbon atoms, cycloalkyl of 3–6 carbon atoms, a 5–7 membered heteroaryl having 1–3 heteroatoms selected from N, NR9, S and O, a 5–7 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, NR9, S and O, or phenyl;

R_9 is hydrogen, alkyl of 1–6 carbon atoms, cycloalkyl of 3–6 carbon atoms, or phenyl;

R_{10} is alkyl of 1–6 carbon atoms, cycloalkyl of 3–6 carbon atoms, phenyl, or 5–7 membered heteroaryl, having 1–3 heteroatoms selected from N, NR9, S and O;

R11 and R12 are, independently, hydrogen, alkyl of 1–6 carbon atoms, cycloalkyl of 3–6 carbon atoms, a 5–7 membered heteroaryl having 1–3 heteroatoms selected from N, NR9, S and O, a 5–7 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, NR9, S and O, or phenyl, and the optional double bond represented by the dotted line is present; or

R11 and R12, together with the carbons to which they are attached, form a 5–10 membered saturated or unsaturated mono or bicyclic cycloalkyl optionally fused to one of a 5 to 7 membered saturated or unsaturated cycloalkyl ring, a 5–7 membered heteroaryl having 1–3 heteroatoms selected from N, NR9, S and O, a 5–7 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, NR9, S and O, phenyl or napthyl rings; or

R11 and R12, together with the carbons to which they are attached form a 5–10 membered saturated or unsaturated mono- or bicyclic heterocycloalkyl having 1–2 heteroatoms selected from N, NR9, S and O, optionally fused to one of a 5–7 membered mono or bi-cyclic heteroaryl having 1–3 heteroatoms selected from N, NR9, S and O, a 5–7 membered saturated or unsaturated cycloalkyl ring or a phenyl or napthyl ring;

the dotted line represents an optional double bond;

and n=0–2; or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein X is SO_2.

3. A compound according to claim 1 wherein X is SO_2 and Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively.

4. A compound according to claim 1 wherein X is SO_2, Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively, and Z is oxygen.

5. A compound according to claim 1 wherein X is SO_2, Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively, Z is oxygen and R_6 and R_7 are hydrogen.

6. A compound according to claim 1 wherein X is SO_2, Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively, Z is oxygen, R_6 and R_7 are hydrogen, and R_8 is —CH_2OH or methyl.

7. A compound according to claim 1 which is selected from the group consisting of

(1R,2R)-2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino]-N-hydroxycyclohexanecarboxamide;

(1R,2R)-2-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxycyclohexanecarboxamide;

3-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxypropanamide;

3-({[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino)-N-hydroxypropanamide;

(1R,2S)-2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxycyclopentanecarboxamide;

(1R,2S)-2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino]N-hydroxycyclopentanecarboxamide;

(Cis)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}amino)-N-hydroxycyclohexanecarboxamide;

(Cis)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}(methyl)amino]-N-hydroxycyclohexanecarboxamide;

(1R,2R,3S,4R)-(Cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl}amino)-N-hydroxybicyclo[2.2.1]heptane-2-carboxamide; and

(1R,2R,3S,4R)-(Cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl}(methyl)amino)-N-hydroxybicyclo[2.2.1]heptane-2-carboxamide.

EXHIBIT A

active compound and a carrier that is inert to the active compound, is non-toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semi-solid emulsions of either the oil in water or water in oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semipermeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

The dosage to be used in the treatment of a specific patient suffering a MMP or TACE dependent condition must be subjectively determined by the attending physician. The variables involved include the severity of the dysfunction, and the size, age, and response pattern of the patient. Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached. Precise dosages for oral, parenteral, nasal, or intrabronchial administration will be determined by the administering physician based on experience with the individual subject treated and standard medical principles.

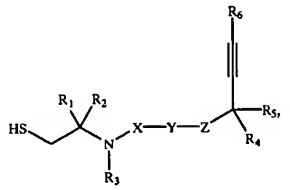
Preferably the pharmaceutical composition is in unit dosage form, e.g., as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage form can be packaged compositions, for example packed powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

What is claimed:

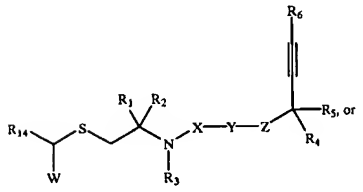
1. The invention provides TACE and MMP inhibitors having the formula:

wherein B is

1a

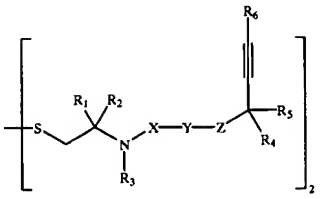


1b



-continued

1c



wherein:

W is oxygen or sulfur;

X is SO_2 or —P(O)—R_{10};

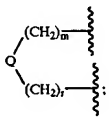
Y is aryl or heteroaryl as defined below, with the proviso that X and Z may not be bonded to adjacent atoms of Y;

Z is O, NH, CH_2 or S;

R_1 is hydrogen, aryl, alkyl of 1–6 carbon atoms, alkenyl of 2–6 carbon atoms, alkynyl of 2–6 carbon atoms;

R_2 is hydrogen, aryl or heteroaryl as defined below, cycloalkyl of 3–6 carbon atoms, —C4–C8-cycloheteroalkyl, alkyl of 1–6 carbon atoms, alkenyl of 2–6 carbon atoms, alkynyl of 2–6 carbon atoms, or $CONR_8R_9$;

or R_1 and R_2, together with the atom to which they are attached, may form a ring wherein R_1 and R_2 represent a divalent moiety of the formula:



wherein

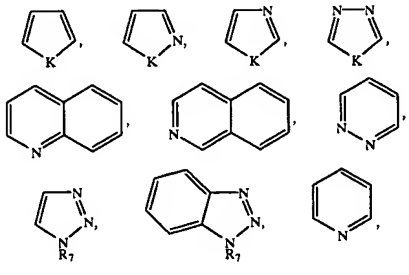
Q=a carbon-carbon single or double bond, O, S, SO, —N—R_{11}, or —$CONR_{15}$;

m=1–3;

r=1 or 2, with the proviso that when Q is a bond, r is equal to 2;

Aryl is phenyl or naphthyl optionally substituted by one to two substituents selected from R_7, where R_7 is as defined below;

Heteroaryl is defined as



administration by intranasal or intrabronchial inhalation or insufflation, the compounds of this invention may be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. The compounds of this invention may also be administered transdermally through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non-toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semi-solid emulsions of either the oil in water or water in oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semipermeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

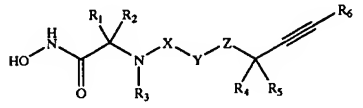
The dosage to be used in the treatment of a specific patient suffering a MMP or TACE dependent condition must be subjectively determined by the attending physician. The variables involved include the severity of the dysfunction, and the size, age, and response pattern of the patient. Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached. Precise dosages for oral, parenteral, nasal, or intrabronchial administration will be determined by the administering physician based on experience with the individual subject treated and standard medical principles.

Preferably the pharmaceutical composition is in unit dosage form, e.g., as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage form can be packaged compositions, for example packed powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

What is claimed:

1. Compounds having the formula:

B



wherein:

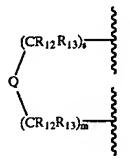
X is SO_2 or —P(O)—R_{10};

Y is aryl or heteroaryl, with the proviso that X and Z may not be bonded to adjacent atoms of Y;

Z is O, NH, CH, or S;

R_2 is hydrogen, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl of 3–6 carbon atoms, piperidinyl, piperazinyl, morpholinyl. tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl, alkyl of 1–6 carbon atoms, alkenyl of 2–6 carbon atoms, alkynyl of 2–6 carbon atoms;

R_1 and R_3, together with the atoms to which they are attached, may form a 6 membered ring wherein R_1 and R_3 represent divalent moieties of the formula:



wherein Q is a carbon-carbon single or double bond, O, S, SO, SO_2, —N—R_{11}, or —$CONR_{14}$:

m=2–3

s is 0–2; provided that Q, s, and m, taken together represent 4 atoms;

R_4 and R_5 are each, independently, hydrogen or alkyl of 1–6 carbon atoms, —CN, or —CCH;

R_6 is hydrogen, aryl, heteroaryl, alkyl of 1–6 carbon atoms, alkenyl of 2–6 carbon atoms, alkynyl of 2–6 carbon atoms, cycloalkyl of 3–6 carbon atoms, piperidinyl piperazinyl, morpholinyl, tetrahydropyranyl, tetrahydrofuranyl, pyrolidinyl;

R_8 and R_9 are each, independently, hydrogen, alkyl of 1–6 carbon atoms, alkenyl of 2–6 carbon atoms, alkynyl of 2–6 carbon atoms, cycloalkyl of 3–6 carbon atoms, aryl, aralkyl, heteroaryl, heteroaralkyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl;

R_{10} is alkyl of 1–6 carbon atoms, cycloalkyl of 3–6 carbon atoms, aryl or heteroaryl;

R_{11} is hydrogen, alkyl of 1–6 carbon atoms, cycloalkyl of 3–6 carbon atoms, aryl, heteroaryl, —$S(O)_nR_8$, —$COOR_8$, —$CONRR_8R_9$, —SO_2 NR_8R_9 or —COR_8;

R_{12} and R_{13} are independently selected from H, —OR_8, —NR_8R_9, alkyl of 1–6 carbon atoms, alkenyl of 2–6 carbon atoms, alkynyl of 2–6 carbon atoms, cycloalkyl of 3–6 carbon atoms, aryl, heteroaryl, —$COOR_8$; —$CONR_8R_9$; or R_{12} and R_{13} together form a —C_3–C_6-cycloalkyl of 3–6 carbon atoms or a —C_5–C_8-cycloheteroalkyl ring; or R_{12} and R_{13},together with the carbon to which they are attached, form a carbonyl group;

R_{14} is hydrogen, aryl, heteroaryl, alkyl of 1–6 carbon atoms or cycloalkyl of 3–6 carbon atoms;

and n is 0–2;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively, or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 wherein Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively, and X is SO_2, or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 1 wherein Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively, X is SO_2, and Z is oxygen, or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 1 wherein Y is a phenyl ring substituted at the 1- and 4-positions by X and Z,

emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, e.g., cellulose derivatives, preferable sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g., glycols) and their derivatives, and oils (e.g., fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Oral administration may be either liquid or solid composition form.

The compounds of this invention may be administered rectally in the form of a conventional suppository. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of this invention may be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. The compounds of this invention may also be administered transdermally through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non-toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semi-solid emulsions of either the oil in water or water in oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semipermeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

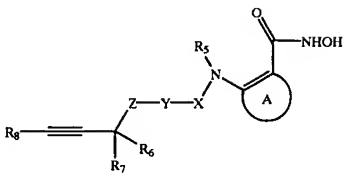
The dosage to be used in the treatment of a specific patient suffering a MMP or TACE dependent condition must be subjectively determined by the attending physician. The variables involved include the severity of the dysfunction, and the size, age, and response pattern of the patient. Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached. Precise dosages for oral, parenteral, nasal, or intrabronchial administration will be determined by the administering physician based on experience with the individual subject treated and standard medical principles.

Preferably the pharmaceutical composition is in unit dosage form, e.g., as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage form can be packaged compositions, for example packed powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

What is claimed:

1. A compound of the formula:

B



where the C(=O)NHOH moiety and the —NR^5— moiety are bonded to adjacent carbons of group A; wherein

A is 5–6 membered heteroaryl having 1 to 3 heteroatoms selected from N, NR9, S and O;

X is SO_2 or —$P(O)R_{10}$;

Y is aryl or 5–10 membered mono- or bi-cyclic heteroaryl having from 1 to three heteroatoms selected from N, NR9, S and O, with the proviso that X and Z may not be bonded to adjacent atoms of Y;

Z is O, NH, CH_2 or S;

R_5 is hydrogen or alkyl of 1–6 carbon atoms;

R_6 and R_7 are each, independently, hydrogen, alkyl of 1–6 carbon atoms, —CN, —CCH;

R_8 is hydrogen, alkyl of 1–6 carbon atoms, alkenyl of 2–6 carbon atoms, alkynyl of 2–6 carbon atoms, cycloalkyl of 3–6 carbon atoms, aryl, 5 to 10 membered heteroaryl having 1 to 3 heteroatoms selected from N, NR9, S and O, or 5 to 9 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, NR9, S and O;

R_9 is hydrogen, aryl, alkyl of 1–6 carbon atoms or cycloalkyl of 3–6 carbon atoms;

and R_{10} is alkyl of 1–6 carbon atoms, cycloalkyl of 3–6 carbon atoms, aryl, or heteroaryl; or a pharmaceutically acceptable salt thereof.

2. A compound of structure B according to claim **1** wherein the ring atom of A adjacent the —NR^5— group is carbon and has a substituent other than hydrogen.

3. A compound according to claim **2** wherein Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively.

4. A compound according to claim **3** wherein X is SO_2.

5. A compound according to claim **3** wherein X is SO_2 and Z is oxygen.

6. A compound according to claim **3** wherein X is SO_2, Z is oxygen, and R_6 and R_7 are hydrogen.

7. A compound according to claim **3** wherein X is SO_2, Z is oxygen, R_6 and R_7 are hydrogen, and R_8 is —CH_2OH or methyl.

8. A compound according to claim **1** which is (3-[methyl-(4-but-2-ynyloxy-benzenesulfonyl-amino]-N-hydroxy-2,6-dimethoxy-isonicotinamide.

9. A compound according to claim **1** which is 3-(4-But-2-ynyloxy-benzenesulfonylamino)-N-hydroxy-2,6-dimethoxy-isonicotinamide.

10. A method of inhibiting pathological changes mediated by TNF-α converting enzyme (TACE) in a mammal in need thereof which comprises administering to said mammal a therapeutically effective amount of a compound having the formula

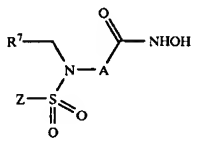
pounds of this invention may also be administered transdermally through the use of a tansdrmal patch containing the active compound and a carrier that is inert to the active compound, is non-toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as crems and ointments, pastes, gels, and occlusive devices. The crews and ointments may be viscous liquid or semi-solid emulsions of either the oil in water or water in oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petoleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semipermeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

The dosage to be used in the treatment of a specific patient suffering from a disease or condition in which MMPs and TACE are involved must be subjectively deterrd by the attending physician. The variables involved include the severity of the dysfunction, and the size, age, and response pattern of the patient. Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached. Precise dosages for oral, parenteral, nasal, or intrabronchial administration will be determined by the admiddering physician based on experience with the individual subject treated and standard medical principles.

Preferably the phartaceutical composition is in unit dosage form, e.g., as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage form can be packaged compositions, for example packed powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

What is claimed:

1. A compound having the formula



where the hydroxanic acid moiety and the sulfonamido moiety are bonded to adjacent carbons on the phenyl or naphthyl ring of group A where:

A is phenyl or naphthyl, optionally substituted by R^1, R^2, R^3 and R^4;

Z is aryl, heteroaryl, orheteroaryl fused to a phenyl,

where aryl is phenyl or naphthyl optionally substituted by R^1, R^2, R^3 and R^4;

heteroaryl is a 5–6 membered heteroaromatic ring having from 1 to 3 heteroatoms independently selected from N, O, and S, and optionally substituted by R^1, R^2, R^3 and R^4;

and when heteroaryl is fused to phenyl, either or both of the rings can be optionally substituted by R^1, R^2, R^3 and R^4;

R^1, R^2, R^3 and R^4 are independently —H, —COR^5, —F, —Br, —Cl, —I, —$C(O)NR^5OR^6$,—CN, —OR^5, -C_1–C_4-perfluoroalkyl, —$S(O)_xR^5$ where x is 0–2, —$OPO(OR^5)OR^6$, —$PO(OR_6)R_5$, —$OC(O)NR^5R^6$, —$COOR^5$, —$CONR^5R^6$, —SO_3H, —NR^5R^6, —NR^5COR^6, —NR^5COOR^6, —$SO_2NR^5R^6$, —NO_2, —$N(R^5)SO_2R^6$, —$NR^5CONR^5R^6$, —$NR^5C(=NR^6)NR^5R^6$, 3–6 membered cycloheteroalkyl having one to three heteroatoms independently selected from N, O, and S and optionally having 1 or 2 double bonds and optionally substituted by one to three groups each selected independently from R^5; -aryl or heterorryl as defined above, biphenyl optionally substituted by one to four groups each selected independently from R^4, —SO_2NHCOR^5 or $CONHSO_2R^5$ where R^5 is not H, -tetrazol-5-yl, —SO_2NHCN, —$SO_2NHCONR^5R^6$ or straight chain or branched -C_1–C_6 alkyl, -C_2–C_6-alkenyl, or -C_2–C_6-alkynyl, or -C_3–C_6-cycloalkyl optionally having 1 or 2 double bonds each optionally substituted with —COR^5, —CN, -C_2–C_6 alkenyl, -C_2–C_6 alkynyl, —OR^5, -C_1–C_4-perfluoroalkyl, —$S(O)_xR^5$ where x is 0–2, —$OC(O)NR^5R^6$, —$COOR^5$, —$CONR^5R^6$, —SO_3H, —NR^5R^6, —NR^5COR^6, —NR^5COOR^6, —$SO_2NR^5R^6$, —NO_2, —$N(R^5)SO_2R^6$, —$NR^5CONR^5R^6$, -C_3–C_6cycloallkyl as defined above, 3–6 membered cycloheteloalkyl as defined above, aryl or heteroaryl as defined above, biphenyl, —SO_2NHCOR^5 or —$CONHSO_2R^5$ where R^5 is not hydrogen; —$PO(OR^5)OR^6$, —$PO(OR^6)R^5$, -tetrazol-5-yl, $C(O)NR^5OR^6$, —$NR^5C(=NR^6)NR^5R^6$, —$SO_2NHCONR^5R^6$ or SO_2NHCN;

with the proviso that when R^1 and R^2 are on adjacent carbons of A, R^1 and R^2 together with the carbons to which they are attached can form a 5 to 7 membered saturated or unsaturated heterocyclic ring or a 5–6 membered heteroaryl ring, each having 1 to 3 heteroatoms independently selected from O, S, or N, and each optionally substituted by one to four groups each selected independently from R^4; or a 5 to 7 membered saturated or unsaturated carbocyclic ring optionally substituted by one to four groups each selected independently from R^4;

R^5 and R^6 are independently H, aryl and heteroaryl as defined above, -C_3–C_6-cycloalkyl as defined above, -C_3–C_6-cycloheteroalkyl as defined above, -C_1–C_4-perfluoroaikyl, or straight chain or branched -C_1–C_6 alkyl, -C_2–C_6-alkenyl, or -C_2–C_6-alkynyl each optionally substituted with —OH, —COR^8, —CN, —$C(O)NR^8OR^9$, -C_2–C_6-alkenyl, -C_2–C_6-alkynyl, —OR^8, -C_1–C_4-perfluoroalkyl, —$S(O)_xR^8$ where x is 0–2, —$OPO(OR^8)OR^9$, —$PO(OR^8)R^9$, —$OC(O)NR^8R^9$, —$COOR^8$, —$CONR^8R^9$, —SO_3H, —NR^8R^9,—$NCOR^8R^9$, —NR^8COOR^9, —$SO_2NR^8R^9$, —NO_2, —$N(R^8)SO_2R^9$, —$NR^8CONR^8R^9$, -C_3–C_6 cycloaalyl as defined above, 3–6 membered cycloheteroalkyl as defined above, aryl or heteroaryl as defined above, —SO_2NHCOR^8 or —$CONHSO_2R^8$ where R^8 is not hydrogen, -tetrazol-5-yl, —$NR^8C(=NR^9)NR^8R^9$, —$SO_2NHCONR^8R^9$, or —SO_2NHCN;

R^7 is hydrogen, straight chain or branched -C_1–C_6-alkyl, -C_2–C_6-alkenyl, or -C_2–C_6-alkynyl each optionally substituted with —OH, —COR^5, —CN, -C_2–C_6-alkenyl, -C_2–C_6-alkynyl, —OR^5, -C_1–C_4-perfluoroalkyl, —$S(O)_xR^5$ where x is 0–2, —$OPO(OR^5)OR^6$, —$PO(OR^5)R^6$, —$OC(O)NR^5R^6$, —$COOR^5$, —$CONR^5R^6$, —SO_3H, —NR^5R^6, —NR^5COR^6, —NR^5COOR^6, —$SO_2NR^5R^6$, —NO_2, —$N(R^5)SO_2R^6$, —$NR^5CONR^5R^6$, -C_3–C_6 cycloalkyl as defined above, -C_3–C_6-cycloheteroalkyl as defined